Detecting latent signals in FDA AERS: paroxetine and pravastatin in combination are associated with an increase in blood glucose

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Supplemental Material

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A Clinical Analysis

Each of the three replication sites (Stanford Hospital, Vanderbilt Hospital, and Partners Healthcare) obtained institutional review board approval for this retrospective clinical analysis at their respective institutions. In sections A1, A2, and A3 we describe the detailed data extraction and clinical analysis methods used at each site. These have small differences based on local database capabilities.

A1 Clinical Analysis at Site 1

A1.1 Inclusion criteria

We extracted clinical data from electronic medical records, in particular blood glucose measurements and prescription orders. Three cohorts of patients were extracted; (1) patients prescribed pravastatin, but not paroxetine, (2) patients prescribed paroxetine, but not pravastatin, and (3) patients prescribed both pravastatin and paroxetine. We refer to these three cohorts as pravastatin-only, paroxetine-only, and combination respectively. In all cases patients may also have been on other medications. The qualification criteria for the combination cohort required patients to be prescribed pravastatin and paroxetine within 36 days of each other. We estimate, conservatively, that a very high proportion of qualified patients will be taking both medications concurrently. We do this since we do not have direct data on patient compliance. Finally, to control for possible medication confounders we excluded any patients diagnosed with diabetes mellitus as determined by the presence of appropriate International Classification of Diseases, 9th edition codes (250.*).

A1.2 Estimating blood glucose concentration from the clinical records

Blood glucose concentration was estimated for each patient as the mean non-fasting blood glucose concentration reported in the clinical records. Figure S1 shows the patient timeline and where blood glucose measurements were extracted in the combination cohort. We estimated baseline blood glucose concentration as the mean non-fasting glucose measurement before the patient started the combination therapy (Figure S1 green area). This estimate was compared to the mean blood glucose measurement taken after the patient started combination therapy (Figure S1 yellow area).

Figure S2 outlines the patient timeline and where blood glucose measurements were extracted in the single drug cohorts (pravastatin-only and paroxetine-only). We estimated the baseline blood glucose concentration as the mean measurement before the drug was prescribed and the therapy blood glucose concentration as the mean measurement after the drug was prescribed.

A2 Clinical Analysis at Site 2

A2.1 Inclusion criteria

We extracted blood glucose concentration measurements from the electronic medical records for patients in three cohorts; (1) pravastatin, but not paroxetine, (2) paroxetine, but not pravastatin, and (3) both pravastatin and paroxetine. These cohorts are referred to as pravastatin-only, paroxetine-only, and combination, respectively. Using previously-validated natural language processing algorithms[1] on the content of the clinical record, we identified patients taking either of these two drugs. To count as a positive instance of the medication, we required the presence of an ingredient (pravastatin or paroxetine) and a drug dose or frequency. We removed mentions of drugs describing adverse effects of these medications. Manual chart review of the combination cohort cases determined that the drug mentions were true positives. We required patients identified as taking both drugs to have a 43 day overlap of the drug combination therapy (Figure S3). Otherwise, we included the patient in one of the single drug populations. Finally, to control for possible medication confounders we excluded any patients diagnosed with diabetes mellitus as determined by the presence of appropriate International Classification of Diseases, 9th edition codes (250.*).

A2.2 Estimating blood glucose concentration from the clinical records

To determine the baseline glucose concentration for each patient, we constructed a timeline extracted from the clinical record that represented the periods of time the patient was on either pravastatin or paroxetine. In the combination cohort the time period that overlaps between the drugs is at least 43 days. The baseline glucose concentration is the mean of the glucose measurements taken in the 36 days preceding the start of the latter drug (Figure S3 green area). We estimated the combination therapy blood glucose concentration as the mean of the glucose measurements taken in time period between day 7 and day 43, inclusive (Figure S3 yellow area). To allow enough time for the combination therapy to present a physiological phenotype we ignore any glucose measurements taken in the six days following the start of the latter drug therapy (Figure S3 gray area).

Figure S4 shows the analogous timeline for the single drug populations. The baseline blood glucose concentration is the mean of the glucose measurements taken in the 36 days preceding the start of the drug therapy, and the post therapy blood glucose concentration is the mean of the glucose measurements taken from day 7 to 43, inclusive. To allow enough time for the therapy to present a physiological phenotype we ignore any glucose measurements taken in the six days immediately following the start of the drug therapy.

A2.3 Statistical analysis

Basic cohort demographic statistics and initial t-tests were performed using Stata version 9.2 (StataCorp, College Station, Texas).

A3 Clinical Analysis at Site 3

A3.1 Inclusion criteria

We extracted blood glucose concentration measurements from the electronic medical records for patients in three cohorts; (1) pravastatin, but not paroxetine, (2) paroxetine, but not pravastatin, and (3) both pravastatin and paroxetine. These cohorts are referred to as pravastatin-only, paroxetine-only, and combination, respectively. Using text-mining on the content of the clinical record we identified patients taking either of these two drugs. We required patients identified as taking both drugs to have a 43 day overlap of the drug combination therapy (Figure S3). Otherwise, we included the patient in one of the single drug populations. The single drug cohorts (pravastatin-only and paroxetine-only) were matched to the combination cohort on sex, age, and race. Finally, to control for possible medication confounders we excluded any patients diagnosed with diabetes mellitus.

A3.2 Estimating blood glucose concentration from the clinical records

To determine the baseline glucose concentration for each patient, we constructed a timeline extracted from the clinical record which represented the periods of time the patient was on either pravastatin or paroxetine. In the combination cohort the time period that overlaps between the drugs is at least 43 days. The baseline glucose concentration is the mean of the glucose measurements taken in the 36 days preceding the start of the latter drug (Figure S3 green area). We estimated the combination therapy blood glucose concentration as the mean of the glucose measurements taken in time period between day 7 and day 43, inclusive (Figure S3 yellow area). To allow enough time for the combination therapy to present a physiological phenotype we ignore any glucose measurements taken in the six days following the start of the latter drug therapy (Figure S3 gray area).

Figure S4 shows the analogous timeline for the single drug populations. These populations were selected to match the distribution of age, sex, and race of the combination therapy group. The baseline blood glucose concentration is the mean of the glucose measurements taken in the 36 days preceding the start of the drug therapy, and the post therapy blood glucose concentration is the mean of the glucose measurements taken from day 7 to 43, inclusive. To allow enough time for the therapy to present a physiological phenotype we ignore any glucose measurements taken in the six days immediately following the start of the drug therapy.

A4 Grouped analysis

We present two alternative pooled analyses that we performed on the combined data from the three sites. Since the type of databases and extraction methods differ slightly from site to site it is important to note that these analyses are an approximation.

A4.1 Proportion of patients with increased glucose

To determine the significance of the number of patients with increased blood glucose in the combination therapy cohort (pravastatin and paroxetine) we performed a chi-squared test. We tested the the ratio of combination patients who had an increase in their blood glucose concentration after starting combination therapy to the ratio of patients that had an increase in their blood glucose after starting single-drug therapies (pravastatin or paroxetine). We found that 61% of patients on the combination therapy had an increase their blood glucose concentration compared to 44% for the pravastatin-only cohort and 45% for the paroxetine-only cohort. We found the ratios of the combination cohort to the pravastatin-only cohort to be significantly different ($p < 0.001$), and also found the ratios of the combination cohort to the paroxetine-only cohort to be significantly different ($p < 0.001$). We combined the two single-therapy cohorts and found that 45% of patients on single-drug therapy had an increase in their blood glucose overall and this ratio was significantly lower than the combination therapy patients ($p < 0.001$).

A4.2 Pooled analysis of three sites

We performed a pooled analysis which combined each cohort (pravastatin-only, paroxetine-only, and combination) across the three sites. IRB restrictions did not allow us to combine the raw clinical data from each patient directly and therefore an ANCOVA could not be performed. However, since the patient cohorts are independent we are able to combine the data under basic normality assumptions, which appear from the data to be appropriate. Using the means and standard deviations of the glucose changes of the cohorts at each of the three sites we calculated the weighted mean (Equation S1) and weighted standard deviation (Equation S2) of glucose changes in the pooled cohorts. The results of this analysis are summarized in Table S5.

$$\mu_{X1\cup\ldots\cup XM} = \frac{\sum_{i=1}^{M} N_{X_i}\mu_{X_i}}{\sum_{i=1}^{M} N_{X_i}} \tag{1}$$

$$\sigma_{X1\cup\ldots\cup XM} = \sqrt{\frac{\sum_{i=1}^{M} N_{X_i}(\sigma_{X_i}^2 + \mu_{X_i}^2)}{\sum_{i=1}^{M} N_{X_i}} - \mu_{X1\cup\ldots\cup XM}^2} \tag{2}$$

A5 Other SSRI and statin combination therapy analysis

A5.1 Determination of class wide effect

To determine if the observed perturbation in glucose was a class-wide effect, that is that it applies to any combination of selective serotonin reuptake inhibitors (SSRI) and statins we extracted patients from the Site 1 who were prescribed sertraline or fluoxetine and any statin except for pravastatin (simvastatin, lovastatin, atorvastatin, or rosuvastatin). To construct the SSRI-statin combination cohort we utilized the same identification technique described in A1.2 and illustrated by Figure S1. We tested the observed change in blood glucose concentration with a paired t-test. In addition, we constructed two more cohorts. The first was comprised of patients prescribed paroxetine in combination with any statin and the next was comprised of patients prescribed pravastatin in combination with any SSRI. Again we used the methods described in A1.2.

A5.2 Other specific SSRI and statin combination therapy analysis

We investigated all pairs of statins and SSRIs individually at Site 1 to test for an effect on measured blood glucose levels using the methods described in B1. Of all the combinations of paroxetine, fluoxetine, or sertraline with pravastatin, atorvastatin, simvastatin, rosuvastatin, or lovastatin (13 pairs), only atorvastatin and fluoxetine and rosuvastatin and sertraline showed an effect on blood glucose, however, neither combination was significant in post-hoc test in the ANCOVA. The full results of this analysis are illustrated in Figure S7 and reported in Tables S3B-D.

A5.3 Power calculation for each SSRI/statin combination

For each of the combinations described in A5 we calculated the power to differentiate a change in blood glucose of 20 mg/dl. We used the sample size and standard deviation with the power.t.test method implemented in the R programming language to calculate these power estimates. These power estimates (Tables S3A-D) demonstrate that in nearly all of these combinations we have a large enough sample size to detect a change in blood glucose similar to that observed for paroxetine and pravastatin.

A6 Results of Clinical Analysis Including Diabetics

A6.1 Individual Site Analysis

We investigated if the effect on blood glucose could also be observed when diabetics are included. The clinical analysis described in B1-4 was repeated for patients both with and without a diabetic ICD9 code in their clinical record. Except this one change all variables and analysis were performed exactly as described in the previous sections. We found that at Site 1 the results were nearly identical (20 mg/dl, $p=0.004$), most likely due to adding only a few patients into the data set. However, at Site 2 we saw no significant effect (4 mg/dl, $p=0.65$) on blood glucose when diabetics are included. It is interesting to note that about half of the patient cohort at Site 2 has been diagnosed with diabetes. This makes the results of the analysis difficult to interpret because of many confounding factors that may be introduced when including diabetic patients. Finally at Site 3 we found that the effect was very significantly exacerbated in diabetics (62 mg/dl, $p<0.001$). These results are summarized in are illustrated in Figure S8.

B Analysis of possible confounding conditions

In this section we analyze some possible confounding factors. In each case we found that the there was no significant bias in the variable examined.

B1 Time of day the patient samples were analyzed

Since our blood glucose concentration estimates were not necessarily performed under fasting conditions, we examined the time of day that the analyses were performed for time biases, which could confound the interpretation of the results. We transformed the lab times for 223 glucose concentration measurements into the hour that the analysis was performed in 24 hour format and plotted the distribution of times of day for before and after combination treatment with pravastatin and paroxetine (Figure S11). To test the null hypothesis that the two distributions were not different we used the non-parametric rank sum test. We found no significant difference in the laboratory times before combination treatment when compared to after treatment ($p=0.62$).

B2 Patient co-prescriptions

Since this is a retrospective analysis of the electronic medical record the patients in our cohorts may be on a variety of other drugs. To rule out these co-prescriptions as confounding variables we performed a simple univariate linear regression analysis. First, we extracted all of the co-prescriptions for the 10 patients in the combination therapy cohort at Site 1, of which 9 had co-prescriptions available for analysis. We then grouped these drugs into their respective drug classes. This allowed us to easily group brand name and generic drugs together. For each drug class we constructed a binary vector which identified which patients were prescribed a drug of that class around the same time they were prescribed pravastatin and paroxetine (within 100 days). We tested 250 drug classes in this manner and established the significance of the regression fit using an ANOVA. No drug class reached significance when correcting for multiple hypothesis testing.

References

1. Xu H, Stenner SP, Doan S, Johnson KB, Waitman LR, Denny JC. MedEx: a medication information extraction system for clinical narratives. J Am Med Inform Assoc 2010;17:19-24.

C Supplementary Figures and Tables

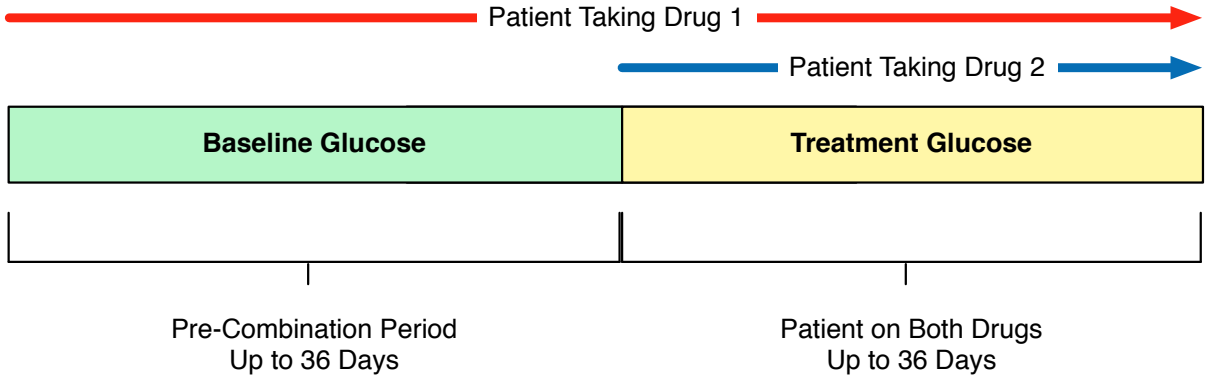

Figure S1. The patient timeline for the combination cohort at Site 1. The baseline blood glucose for each patient was the mean glucose measurements taken before combination therapy started (green area). Blood glucose after combination therapy was the mean blood glucose measurement after the patient started on both drugs (yellow area). We included patients regardless of which drug (pravastatin or paroxetine) was prescribed first.

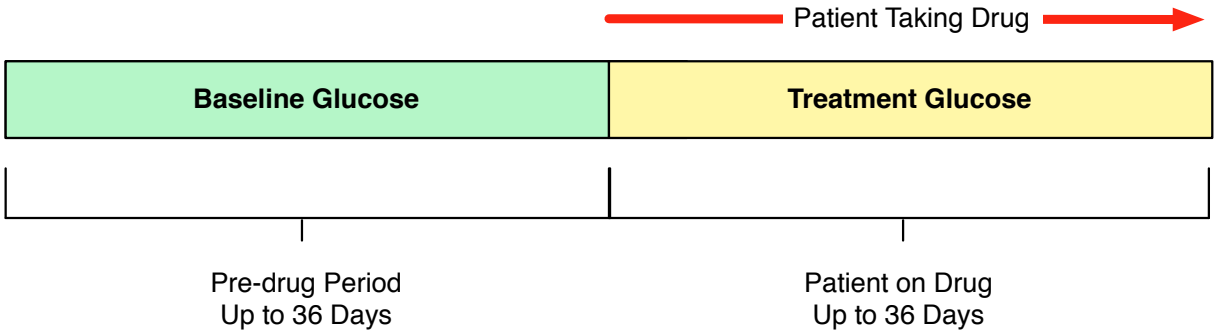

Figure S2. The patient timeline for patients on single drug therapy in the single-drug cohorts at Site 1 (pravastatin-only and paroxetine-only). The baseline blood glucose concentration was the mean glucose measurement before the patient started on the drug (green area), and the blood glucose after starting the drug was the mean measurement after starting the drug (yellow area).

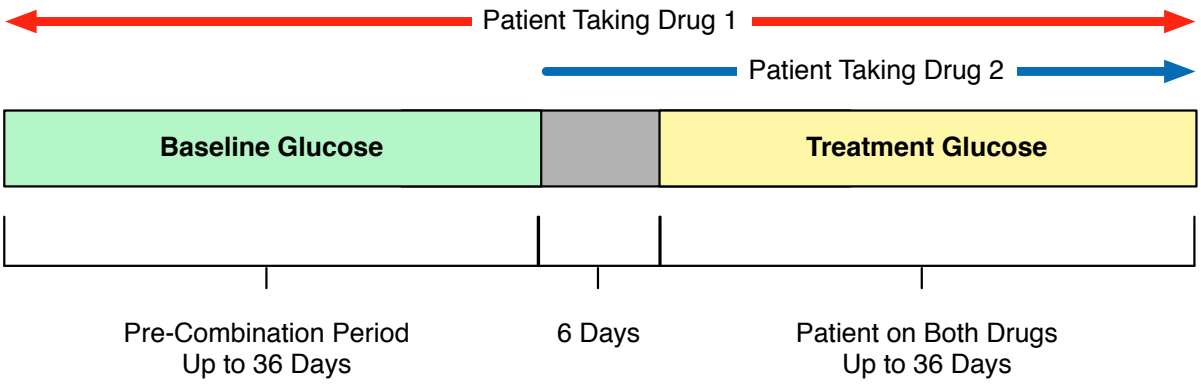

Figure S3. The patient timeline for the combination patient cohort used for the sites 2 and 3. We estimate the baseline blood glucose concentration as the mean of the glucose measurements taken in the 36 days preceding the start of the second drug (green area). The treatment blood glucose concentration is estimated as the mean of the glucose measurements taken from day 7 to day 43, inclusive, after starting the combination therapy (yellow area). Glucose measurements in the 6 days between the start of the second drug are ignored to allow time for the physiological effect to be observed. We included patients regardless of which drug (pravastatin or paroxetine) was prescribed first.

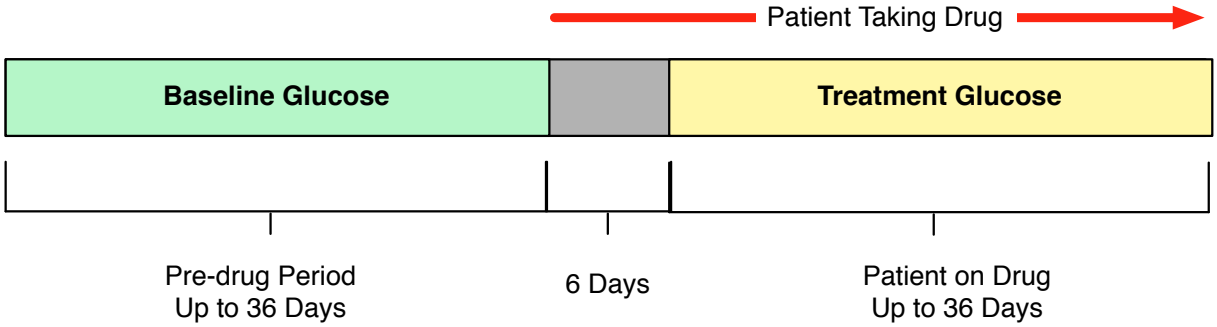

Figure S4. The patient timeline for the single drug patient cohorts at the sites 2 and 3 (pravastatin-only and paroxetine-only). The red arrow indicates the time period the patient is on the drug. We estimate the baseline glucose concentration as the mean of the glucose measurements in the 36 days preceding the start of the single drug therapy (green area), and the post treatment is the mean of the glucose measurements taken from day 7 to 43, inclusive, after start of the single drug therapy (yellow area).

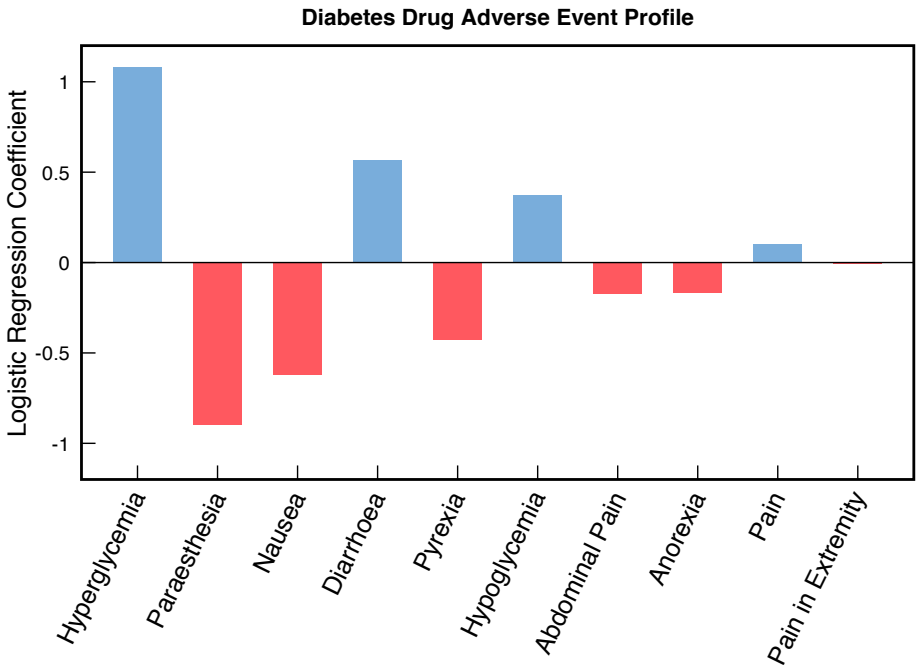

Figure S5. Latent Signal Detection derived profile for diabetes-related adverse events. Each bar represents a normalized logistic regression coefficient. Positive coefficients are shown in blue and negative coefficients are shown in red.

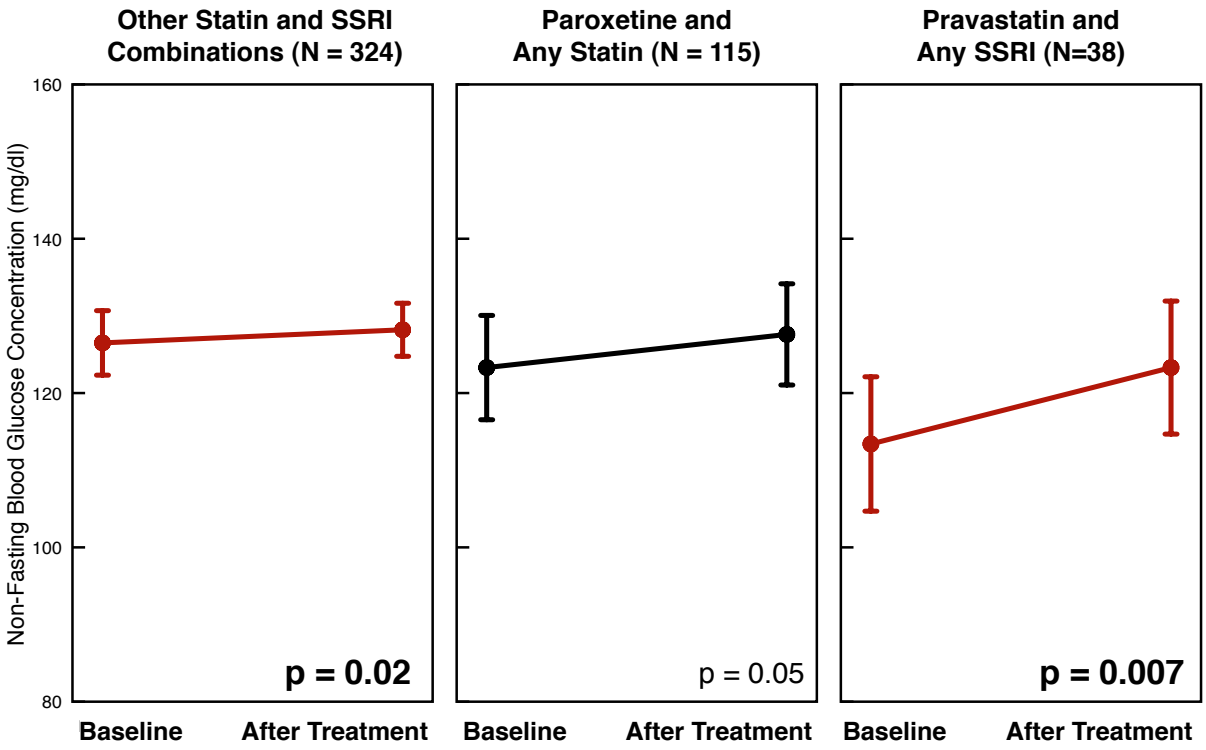

Figure S6. Testing the class-wide effects of statins and SSRIs. The first plot from the shows the change in non-fasting blood glucoses for patients on at least one statin other than pravastatin (atorvastatin, lovastatin, rosuvastatin, or simvastatin) and on at least one SSRI other than paroxetine (fluoxetine or sertraline). The p-values are the result of a paired t-test (after treatment - baseline) on the blood glucoses. The error bars represent 95% confidence intervals. Significant perturbations in blood glucoses are shown in red. If found significant in the t-test an ANCOVA was performed, however, neither of the combinations were significant in post-hoc tests versus individual treatments.

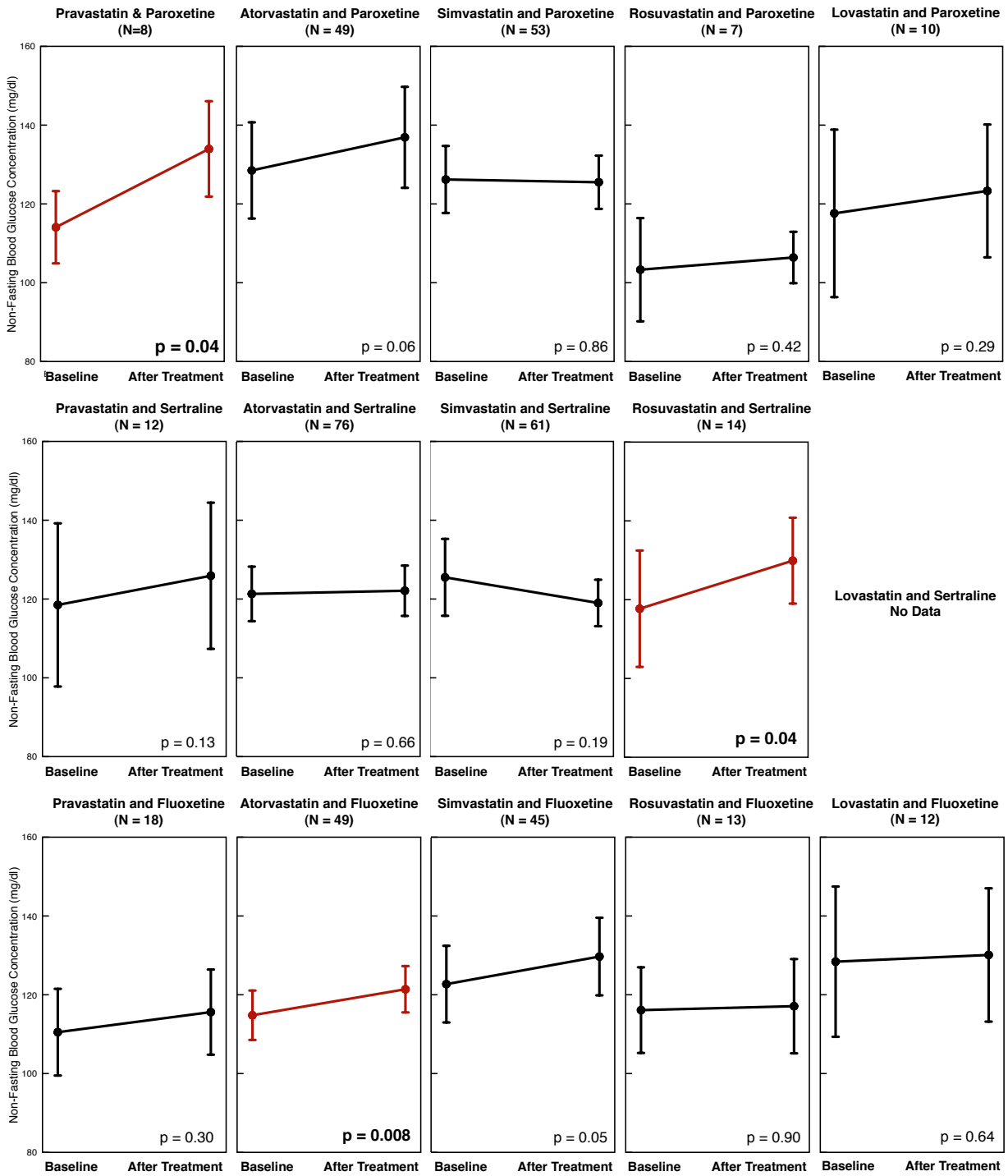

Figure S7. Comparison of change in measured blood glucose for patients prescribed all possible combinations of statins (atorvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin) and selective serotonin re-uptake inhibitors (paroxetine, fluoxetine, and sertraline). The p-values displayed are the result of a paired t-test of the log-transformed glucose values (after treatment - baseline) for the patient cohort. The error bars represent 95% confidence intervals. Significant perturbations in blood glucoses are

shown in red. Significant perturbations were followed up with a full ANCOVA, however, none of the combinations, besides paroxetine and pravastatin, were significant in post-hoc tests.

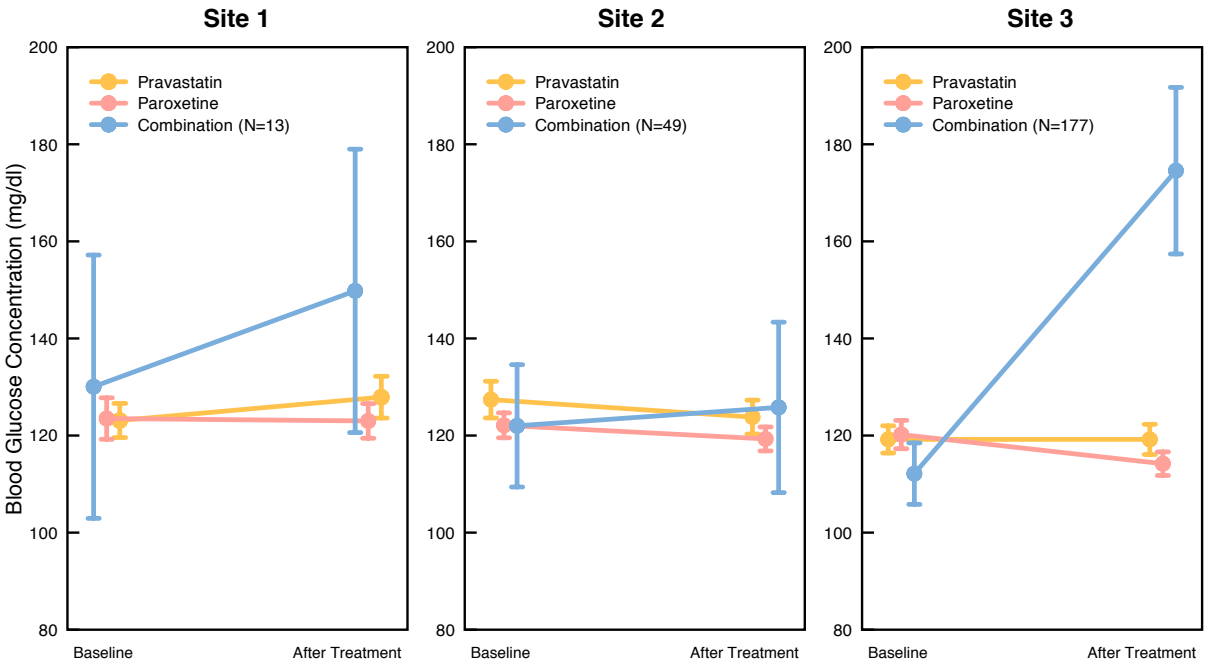

Figure S8. Mean baseline and after treatment blood glucose concentrations with 95% confidence intervals for three independent replication sites including diabetic patients in the cohorts. Each site contains three patient cohorts, pravastatin-only (yellow), paroxetine-only (pink), and pravastatin and paroxetine (blue). Site 3 contained the largest cohort on both pravastatin and paroxetine (N=177), followed by Site 2 (N=49), and Site 1 (N=13). A significant increase in glucose was observed for the patients taking the combination of pravastatin and paroxetine at both Site 1 (20 mg/dl, p=0.004) and Site 3 (62 mg/dl, p<0.001). However, the combination cohort at Site 2 did not show a significance increase of blood glucose post treatment (4 mg/dl, p=0.65).

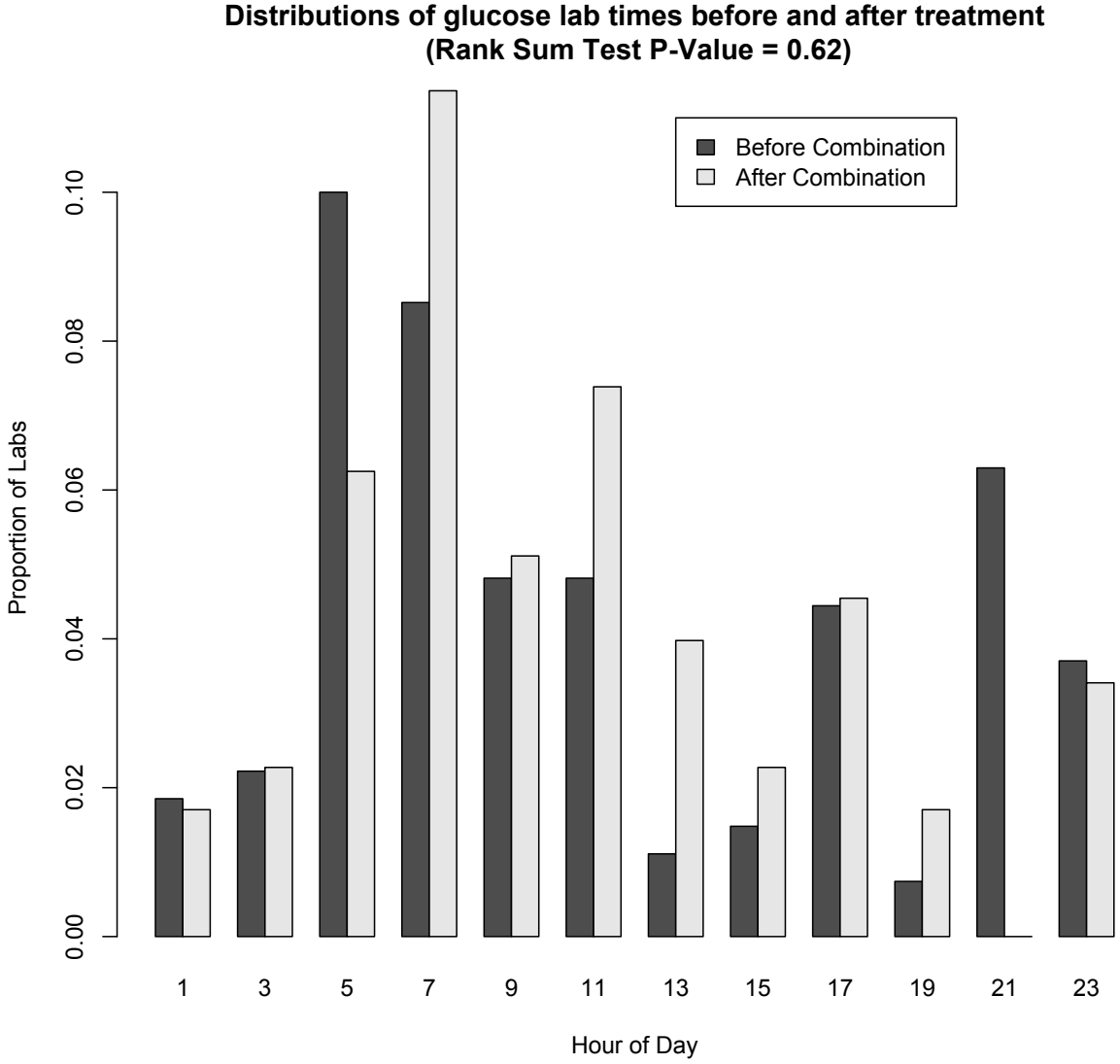

Figure S9. Distribution of the hour each glucose laboratory analysis was performed for both before (dark gray) and after (light gray) treatment with pravastatin and paroxetine. No significant difference (p=0.62) was found between the two distributions using the non-parametric rank sum test.

Table S1. Pairs of drugs predicted to have diabetes related interaction effects by Latent Signal Detection

Drug 1	Drug 2	Score	Z-Score	P-Value
Mefloquine	Sertraline	41.19	706.59	P < 1e-16
Allopurinol	Bendamustine	8.58	209.55	P < 1e-16
Acetaminophen	Trastuzumab	8.17	203.40	P < 1e-16
Paroxetine	**Pravastatin**	**6.87**	**183.61**	**P < 1e-16**

Table S2. Training and testing error for the logistic regression algorithms trained on up to 15 features

Number of Features	Training Error	Test Error
1	0.0485	0.0485
2	0.0485	0.0485
3	0.0401	0.0405
4	0.04	0.0405
5	0.04	0.0405
6	0.04	0.0405
7	0.0398	0.0403
8	0.0398	0.0403
9	0.0221	0.0237
10	0.0206	0.0225
11	0.0205	0.0226
12	0.0203	0.0226
13	0.0202	0.0227
14	0.0199	0.0225
15	0.0195	0.0221

Table S3A. Demographic and Clinical Characteristics of Cohorts of Patients on SSRIs and statins

SSRI	**Sertraline or Fluoxetine**	**Paroxetine**	**Paroxetine, Sertraline, or Fluoxetine**
Statin	**Atorvastatin, Simvastatin, Rosuvastatin, or Lovastatin**	**Atorvastatin, Simvastatin, Rosuvastatin, or Lovastatin**	**Pravastatin**
N	324	115	38
Demographics			
Age (mean ± SD)	66.9 ± 13.6	67.9 ± 13.5	61.2 ± 16.4
Sex (% Female)	57 †	56†	55
Race (% of group)			
White	65	62	71
African American	3	3	5
Hispanic	7	0	0
Other	25	36	24
Glucose (mg/dl mean ± SD)			
Baseline (base)	126.5 ± 38.4 †	123.3 ± 37.0	113.5 ± 27.4
After treatment(s) (post)	128.2 ± 31.6	127.6 ± 35.9	123.0 ± 27.1
Change (base to post)	1.7 ± 27.1 †	4.2 ± 30.3	9.5 ± 20.2
paired t-test (t: post - base)	**0.02**	**0.05**	**0.008**
N patients with glucose increase (% of group)	164 (51)	57 (50)	20 (53)
Statistical Test Power to Observe a Change of 20 mg/dl.	1.00	1.0	1.0

† Identifies values which are significantly ($p \leq 0.05$) different when compared to the corresponding values under Pravastatin and Paroxetine Combination therapy.

Table S3B. Demographic and Clinical Characteristics of Cohorts of Patients on SSRIs and statins

SSRI	**Paroxetine**				
Statin	**Pravastatin**	**Atorvastatin**	**Simvastatin**	**Rosuvastatin**	**Lovastatin**
N	10	49	53	7	10
Demographics					
Age (mean ± SD)	59.9 ± 11.09	68.0 ± 13.7	69.8 ± 14.6 †	60.9 ± 17.2	68.0 ± 8.9
Sex (% Female)	90	55	55	57	60
Race (% of group)					
White	50	67	60	71	40
African American	20	4	4	0	0
Hispanic	0	2	4	14	0
Other	30	27	32	14	60
Glucose (mg/dl mean ± SD)					
Baseline (base)	114.08 ± 14.79	128.5 ± 43.6	126.2 ± 31.6	103.3 ± 17.7	117.6 ± 34.3
After treatment(s) (post)	133.96 ± 19.54	136.9 ± 45.8	125.5 ± 25.1	106.4 ± 8.8 †	123.3 ± 27.2
Change (base to post)	19.88 ± 21.04	8.4 ± 36.0	-0.7 ± 25.4 †	3.1 ± 12.5	5.7 ± 18.0
paired t-test (t: post - base)	**0.04**	**0.06**	**0.86**	**0.42**	**0.29**
N patients with glucose increase (% of group)	8 (80)	26 (54)	24 (45)	5 (71)	4 (40)
Statistical Test Power to Observe a Change of 20 mg/dl.	0.52	0.78	0.98	0.78	0.65

† Identifies values which are significantly ($p \leq 0.05$) different when compared to the corresponding values under Pravastatin and Paroxetine Combination therapy.

Table S3C. Demographic and Clinical Characteristics of Cohorts of Patients on SSRIs and statins

SSRI	**Sertraline**			
Statin	**Pravastatin**	**Atorvastatin**	**Simvastatin**	**Rosuvastatin**
N	12	76	61	14
Demographics				
Age (mean ± SD)	57.8 ± 15.9	71.4 ± 12.7 †	69.1 ± 13.9 †	56.9 ± 10.1
Sex (% Female)	67	57	51 †	57
Race (% of group)				
White	83	63	64	71
African American	0	8	3	0
Hispanic	0	13	5	7
Other	17	16	28	21
Glucose (mg/dl mean ± SD)				
Baseline (base)	118.5 ± 36.6	121.3 ± 30.8	125.5 ± 38.9	117.7 ± 28.2
After treatment(s) (post)	125.9 ± 32.8	122.1 ± 28.4	119.0 ± 23.5	129.9 ± 20.8
Change (base to post)	7.4 ± 16.4	0.8 ± 24.9 †	-6.5 ± 28.2 †	12.2 ± 21.5
paired t-test (t: post - base)	**0.13**	**0.66**	**0.19**	**0.04**
N patients with glucose increase (% of group)	6 (50)	34 (47)	25 (41) †	10 (71)
Statistical Test Power to Observe a Change of 20 mg/dl.	0.84	1.0	0.97	0.64

† Identifies values which are significantly ($p \leq 0.05$) different when compared to the corresponding values under Pravastatin and Paroxetine Combination therapy.

Table S3D. Demographic and Clinical Characteristics of Cohorts of Patients on SSRIs and statins

SSRI	**Fluoxetine**				
Statin	**Pravastatin**	**Atorvastatin**	**Simvastatin**	**Rosuvastatin**	**Lovastatin**
N	18	49	45	13	12
Demographics					
Age (mean ± SD)	62.7 ± 18.6	68.1 ± 12.2	66.5 ± 14.1	65.6 ± 7.0	60.9 ± 12.4
Sex (% Female)	33 †	63	64	62	75
Race (% of group)					
White	67	65	62	69	25
African American	11	2	0	0	8
Hispanic	0	4	9	8	17
Other	22	29	29	23	50
Glucose (mg/dl mean ± SD)					
Baseline (base)	110.5 ± 23.8	114.8 ± 22.4	122.7 ± 33.3	116.1 ± 20.0	128.4 ± 33.7
After treatment(s) (post)	115.6 ± 23.4 †	121.4 ± 21.0	129.7 ± 33.7	117.1 ± 22.0	130.1 ± 29.9
Change (base to post)	5.1 ± 19.1	6.6 ± 17.1	6.97 ± 24.1	1.0 ± 22.4	1.6 ± 16.6 †
paired t-test (t: post - base)	**0.30**	**0.008**	**0.05**	**0.90**	**0.64**
N patients with glucose increase (% of group)	8 (44)	33 (67)	30 (67)	4 (31) †	5 (42)
Statistical Test Power to Observe a Change of 20 mg/dl.	0.87	1.0	0.97	0.60	0.79

† Identifies values which are significantly ($p \leq 0.05$) different when compared to the corresponding values under Pravastatin and Paroxetine Combination therapy.

Table S4. Patient prescription counts of pravastatin and paroxetine at three sites

Drug	Site 1	Site 2	Site 3	Total
Pravastatin	1536	11456	31962	44954
Paroxetine	1910	28092	37863	67865
Pravastatin & Paroxetine	38	821	1737	2596
% of Pravastatin	2.4%	6.7%	5.2%	5.5%
% of Paroxetine	2.0%	2.8%	4.4%	3.7%